IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	FAGER, Gunnar
Serial No.	:	10/098,625
Filed	:	March 18, 2002
For	:	NEW DIALYSIS METHOD
Examiner	:	KIM, Sun U
Art Unit	:	1723
Conf. No.	:	3908

DECLARATION UNDER 37 C.F.R. § 1.132

I, GUNNAR FAGER, declare as follows:

1. I received my MD degree from the Medical Faculty, Göteborg University, Sweden in 1968. I qualified as an Authorised Physician in 1968, and attained specialist qualifications (internal medicine and cardiology) in 1972 and 1974, respectively. I received my PhD in 1979 and was appointed an Associate Professor in Internal Medicine, Sahlgrenska University Hospital, Göteborg, Sweden in 1982. Since 1991, I have been

employed by the assignee of the above referenced application, AstraZeneca AB (formerly Astra Hässle AB), at their R&D department in Mölndal, Sweden, initially as a Senior Medical Adviser and, in 2002, as Scientific Director, Experimental Medicine. I have authored or co-authored many scientific publications, presentations, journal articles and presentations at symposia. My curriculum vitae is attached as Exhibit A.

2. As the inventor in the present case, I was directly involved in the studies that led to the present invention and which are disclosed in the instant specification. I also directly supervised the experiments that yielded the data set forth herein.

3. I have read and understood the content of the pending office action in the present application as well as the prior art that has been cited by the examiner.

4. As stated in the instant specification at page 3, lines 4 to 6, the object of the present invention is to provide an alternative, and preferably safer, more reliable and/or more efficacious, anticoagulant effect during hemodialysis. This object is met by way of the invention as claimed in the main claim that will be filed at the same time as this declaration, which relates to a method of dialysis in which a low molecular weight thrombin inhibitor is added to the dialysing solution prior to and/or during that dialysis (see also page 3, lines 24 to 27 of the instant specification).

5. At paragraph 8 of the office action, the examiner has rejected a claim directed to this method (amongst others) on the basis that it is unpatentable under 35 USC 103(a) over French Patent No. 2,687,070

(hereinafter "FR '070") in view of WO 94/29366 or WO 97/30073 and WO 97/39770. FR '070 teaches a dialysis concentrate containing sodium heparinate, which is used to make up a dialysis solution for use in hemodialysis. The examiner alleges that it would have been obvious for a skilled person to substitute a low molecular weight thrombin inhibitor, such a melagatran or inogatran, for sodium heparinate in the dialysis concentrate of FR '070 in the light of the teachings of the three above-mentioned WO documents.

6. I disagree with this allegation. As can be seen from the Material Safety Data Sheet attached as Exhibit B, sodium heparinate, as employed in the Examples of FR '070 (see page 3, fourth to last line to page 5, line 3 of the English translation thereof) has a molecular weight of *ca* 12,000. Even the low molecular weight heparins (which are not exemplified in the above-referenced passages in FR '070) have molecular weights in the region 2,500 to 8,000 (see page 3, line 3 of the translation). By way of contrast, the term of art "low molecular weight thrombin inhibitor" will be understood by the person of ordinary skill to encompass compounds that inhibit thrombin and have a molecular weight below 2,000, more preferably below 1,000 (see page 7, lines 4 to 10 of the instant specification). Thus, the compounds referred to in the present claims are quite different in their character to those exemplified in FR '070.

7. Further, in my view, there is no motivation provided by any of the three cited WO documents to substitute a low molecular weight thrombin inhibitor for sodium heparinate as taught by FR '070.

8. This notwithstanding, we have performed experiments which demonstrate unequivocally that, by providing a low molecular weight thrombin inhibitor, such as melagatran, to the dialysing solution prior to and/or during dialysis in accordance with in the presently-claimed method, not only can problems associated with standard prior art methodology (see page 2, lines 17 to page 3, line 2 of the instant specification) be solved, but also distinct and unexpected advantages are observed for such inhibitors when compared to the compounds and methodology described in FR '070. I shall now describe these experiments in detail.

9. Figure 5 of the instant specification shows a schematic drawing of a typical hemodialysis set up. Two laboratory bench comparative investigations were designed in order to compare:

(a) the transfer of unfractionated standard sodium heparinate (SH; heparin sodium; as exemplified in FR '070; Leo Pharma AB, Malmö, Sweden) with that of the low molecular weight thrombin inhibitor, melagatran; and

(b) a low molecular weight heparin (MW >3000; mean 5000; Fragmin®; Pharmacia & Upjohn, Stockholm, Sweden) with melagatran.

10. In each comparative experiment, a Dicea 170G (Baxter Healthcare Corp., McGraw Park, IL) dialysis filter was connected to Gambro AK-100 (Gambro) dialysis equipment, in accordance with Figure 1 of the instant specification, and was primed for 15 minutes with dialysis fluid prepared from Biosol A201.5 glucose 5 (Pharmalink, Solna, Sweden) concentrate by a dilution of 1:35 (1+34). The dialysis fluid was passed on one side of the membrane (here designated as the Donor side) at a flow of 500 mL/min. Simultaneously, a physiological saline solution was pumped

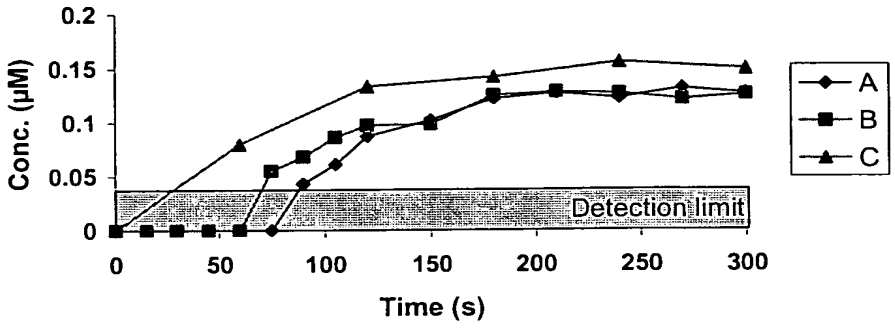
through the other (i.e. the "patient") side (here designated as the Recipient side) of the membrane at 100 mL/min (in the case of the SH comparison), and 250 mL/min (in the case of the Fragmin comparison). The flows on the two sides of the membrane were anti-parallel. The saline solution was then discarded without re-circulation.

11. In both experiments, the pumps were then stopped and the dialysis concentrate was replaced by a new bag of concentrate containing 17,500 IU/L of SH (in the case of the first experiment) or Fragmin (in the case of the second), and, in both comparisons, 3 mg/L (7 μM) of melagatran. These initial concentrations provided final concentrations of about 500 IU/L (SH/Fragmin) and 0.2 μM (melagatran) after a 1+34 dilution. The pumps were restarted at the same speeds, shunting the dialysis fluid *via* a collateral circuit past the filter unit. Filter perfusion was resumed at zero time and samples (*ca.* 2 mL) were collected from the tubing at position A (see Figure 1 of the instant specification; outlet on Recipient side), position B (outlet on Donor side) and position C (inlet on Donor side) at pre-determined time points over 5 minutes.

12. Anti-Factor Xa (anti-FXa) activity (for SH/Fragmin determination) and melagatran concentrations were measured in the collected samples. Anti-FXa activity was determined using a COATEST® Heparin Kit (Chromogenix, Milan, Italy) modified for microtiter plates. Melagatran concentrations were determined using liquid chromatography-mass spectrometry. Blank (before start of filter perfusion) values were subtracted in the heparin assays. Values below the limit of quantification (37 nM melagatran and 0.05 U/mL anti-FXa activity) were set to zero.

13. In both comparisons, in the case of melagatran, experimental steady states were reached within 1 to 2 minutes. Concentrations of melagatran of about 0.15 μM (in the SH comparison) and 0.16 μM (in the Fragmin comparison) were achieved at inlet C on the Donor side, which, in both cases, were close to expectations. Simultaneously, the concentration of melagatran at outlet B on the Donor side levelled off at about 0.13 μM (SH comparison) and 0.11 μM (Fragmin comparison). This suggested that the concentration of melagatran fell by about 0.02 μM and 0.05 μM, respectively. On the Recipient side, melagatran increased to a plateau at about 0.13 μM after 3 minutes (SH comparison) and 0.08 μM after 1 minute (Fragmin comparison). These findings were compatible with anti-parallel flows on the two sides of the membrane; fresh saline solution constantly entering on the Recipient side of the membrane during this experiment was first exposed to the low concentration of melagatran in the outlet end on the Donor side and then to increasing concentrations towards the inlet. Consequently, the concentration on the Recipient side increased from 0 to 0.13 μM (SH comparison) and 0 to 0.08 μM (Fragmin comparison) along the length of the membrane. At the same time, the concentration on the Donor side decreased from 0.15 to 0.13 μM (SH comparison) and 0.16 to 0.11 μM (Fragmin comparison) due to the anti parallel flows. The melagatran results from the SH comparison are shown in Fig. 1 below. Those from the Fragmin comparison showed a similar trend.

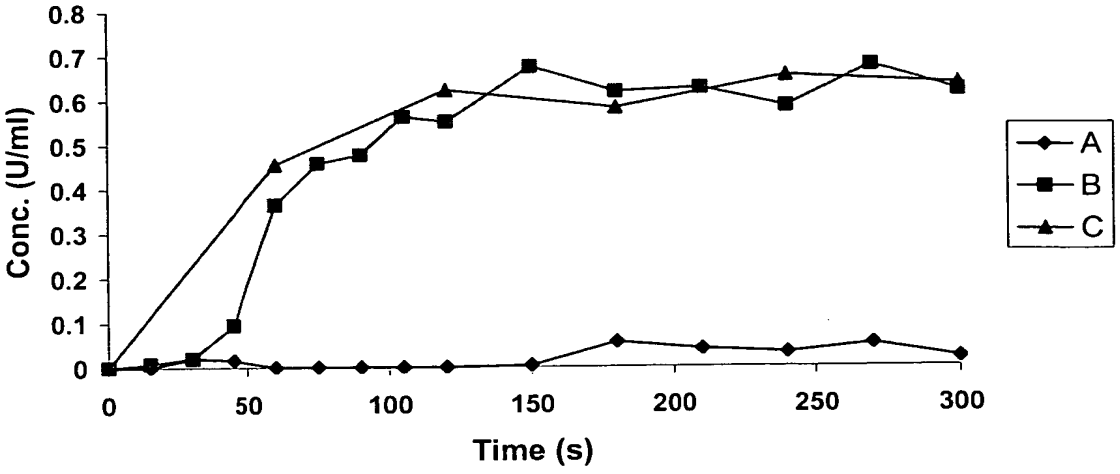
Fig. 1



Concentrations of melagatran (SH comparison experiment) in the inlet C (triangles) and outlet B (squares) on the Donor side and outlet A on the Recipient side (diamonds) against time after start of filter perfusion.

14. By way of a contrast, for SH, within 2 minutes of filter perfusion, the anti-FXa activity had reached a plateau at about 0.6 U/ml in the filter outlet (B) on the Donor side (see Fig. 2 below). The level is almost the same as that in the inlet (C) on the Donor side. This suggested that SH was not transferred from the Donor side fluid during the session. A very low anti-FXa activity was seen in the outlet (A) on the Recipient side, indicating that negligible amounts of SH passed through the dialysis filter.

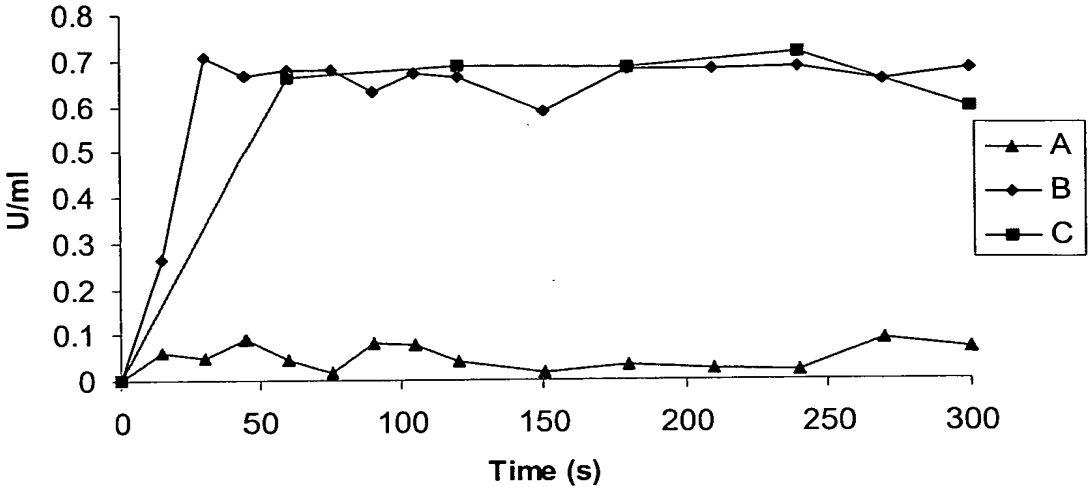
Fig. 2



Anti-Factor Xa activity as a measure of SH concentrations in the inlet C (triangles) and outlet B (squares) on the Donor side and outlet A on the Recipient side (diamonds) against time after start of filter perfusion.

15. Similarly for Fragmin, within 30 seconds of filter perfusion, the anti-FXa activity had reached a plateau at about 0.7 U/ml in the filter outlet (B) on the Donor side (see Fig. 3 below). Again, this level was almost the same as that in the inlet (C) on the Donor side. This suggested that Fragmin was not transferred from the Donor side fluid during the session. A very low anti-FXa activity was seen in the outlet (A) on the Recipient side, again indicating that negligible amounts of Fragmin passed through the dialysis filter.

Fig. 3

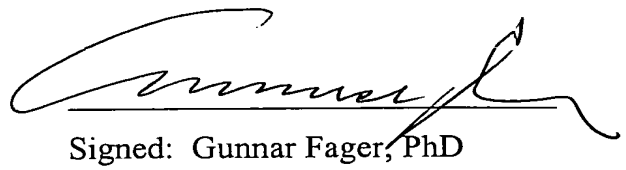


Anti-Factor Xa activity as a measure of Fragmin concentrations in the inlet C (squares) and outlet B (diamonds) on the Donor side and outlet A on the Recipient side (triangles) against time after start of filter perfusion.

16. In conclusion, these results demonstrate that low molecular weight thrombin inhibitors, such as melagatran, may be delivered by way of a dialysing solution during hemodialysis and pass through dialysis filters. This is in complete contrast to both SH and Fragmin, where, despite what is stated in the cited prior art document, FR '070, the current results clearly show that delivery of those compounds by way of a dialysis solution prior to and/or during dialysis will not provide requisite concentrations of active substance in patient plasma to prevent clotting in blood lines and on the filter. In this way, a clear advantage is observed

for the method claimed in the instant application that could not have been foreseen from the prior art cited by the examiner. In my view, the experiments detailed herein clearly show that the presently-claimed invention is patentable over the cited prior art.

17. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further, that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issued thereon.

Date: 4/12/2005 

Day Month Year Signed: Gunnar Fager, PhD

Place: Mölndal, Sweden

Attachments

Exhibit A

Exhibit B

EXHIBIT A

CURRICULUM VITAE

Gunnar Fager MD PhD
Born March 26, 1941

Current position:

Scientific Director, Experimental Medicine, AstraZeneca R&D Mölndal, S-431 83 Mölndal, Sweden.

Acad. History:

Med.Lic. 1968 (MD)
Leg.Läk. 1968 (Authorised physician)
Spec. invärtesmedicin 1972 (Specialist Internal Medicine)
Spec. kardiologi 1974 (Specialist Cardiology)
Med. Dr. 1979 (Ph D)
Docent 1982 (Associate Professor)

Professional experience:

Previous positions:	Junior physician in internal medicine (6.5 years) and cardiology (4 years) and senior physician in internal medicine (8.5 years) and cardiology (2 years) at Sahlgren's Hospital, Göteborg. Senior researcher at the Wallenberg Laboratory for Cardiovascular Research, Göteborg.
Present position:	Since 1991 Senior Medical Adviser and since 2002 Scientific Director, Experimental Medicine, AstraZeneca R&D Mölndal.
Editorial Boards:	Member of board of reviewers of Arteriosclerosis, Thrombosis and Vascular Biology, Journal of Internal Medicine, Atherosclerosis

Teaching and supervising experience:

Associate Professor Internal Medicine (1982). Involved in education of medical students (lectures, seminars, demonstrations and bed-side education) and specialist-degree trainees in internal medicine (about 10 years) and cardiology (about 10 years). 'Klinisk amanuens' 2 years.

Tutor of Alexandra Krettek (Diss. 1999; Expression of platelet-derived growth factor isoforms and their receptors in cells accumulating in the human atherosclerotic lesion).

Currently tutor of two Ph.D. students:

Paula Morelli (Wallenberg Lab.)

Corina Dota (Division of Cardiology)

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Gunnar Fager
October 2003

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EXHIBIT B

MSDS Number: **H0314** * * * * * *Effective Date: 02/18/03* * * * * *Supercedes: 05/08/00*

MSDS Material Safety Data Sheet

From: Mallinckrodt Baker, Inc.
222 Red School Lane
Phillipsburg, NJ 08865

J.T.Baker®

24 Hour Emergency Telephone: 908-859-21
CHEMTREC: 1-800-424-9300
National Respons In Canada
CANUTEC: 613-996-6666
Outside U.S. And Canada
Chemtrec: 703-527-3887

NOTE: CHEMTREC, CANUTEC and Nationa Response Center emergency numbers to b used only in the event of chemical emergencies involving a spill, leak, fire, exposure or accident involving chemicals.

All non-emergency questions should be directed to Customer Service (1-800-582-2537) for assistance.

HEPARIN, Na

1. Product Identification

Synonyms: Sodium heparin; Heparin, sodium salt; sodium acid heparin; sodium heparinate
CAS No.: 9041-08-1
Molecular Weight: ca. 12000
Chemical Formula: ca. (C12H16NS2Na3)20
Product Codes: M916

2. Composition/Information on Ingredients

Ingredient	CAS No	Percent	Hazardous
Sodium Heparin	9041-08-1	98 - 100%	Yes

3. Hazards Identification

Emergency Overview

WARNING! MAY BE HARMFUL IF SWALLOWED, INHALED OR ABSORBED THROUGH SKIN. MAY CAUSE IRRITATION TO SKIN, EYES, AND RESPIRATORY TRACT.

Potential Health Effects

Information on the human health effects from exposure to this substance is limited.

Inhalation:
No information found, but compound should be handled as a potential health hazard. May cause irritation to the respiratory tract. Symptoms may include coughing, sore throat, labored breathing, and chest pain.
Ingestion:
No information found, but compound should be handled as a potential health hazard. May cause irritation to the gastrointestinal tract. Symptoms may include nausea, vomiting and diarrhea.
Skin Contact:
No information found, but compound should be handled as a potential health hazard. May cause irritation with redness and pain. May be absorbed through the skin with possible systemic effects.
Eye Contact:
No information found, but compound should be handled as a potential health hazard. May cause irritation, redness and pain.
Chronic Exposure:
No information found.
Aggravation of Pre-existing Conditions:
No information found.

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4. First Aid Measures

Inhalation:
Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention.
Ingestion:
Give large amounts of water to drink. Never give anything by mouth to an unconscious person. Get medical attention.
Skin Contact:
Immediately flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention if symptoms occur.
Eye Contact:
Immediately flush eyes with plenty of water for at least 15 minutes, lifting upper and lower eyelids occasionally. Get medical attention if irritation persists.

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5. Fire Fighting Measures

Fire:
As with most organic solids, fire is possible at elevated temperatures or by contact with an ignition source.
Explosion:
Fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source is a potential dust explosion hazard.
Fire Extinguishing Media:

Water spray, dry chemical, alcohol foam, or carbon dioxide.
Special Information:
In the event of a fire, wear full protective clothing and NIOSH-approved self-contained breathing apparatus with full facepiece operated in the pressure demand or other positive pressure mode.

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6. Accidental Release Measures

Remove all sources of ignition. Ventilate area of leak or spill. Wear appropriate personal protective equipment as specified in Section 8. Spills: Clean up spills in a manner that does not disperse dust into the air. Use non-sparking tools and equipment. Reduce airborne dust and prevent scattering by moistening with water. Pick up spill for recovery or disposal and place in a closed container.

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7. Handling and Storage

Keep in a tightly closed container, stored in a cool, dry, ventilated area. Protect against physical damage. Isolate from incompatible substances. Containers of this material may be hazardous when empty since they retain product residues (dust, solids); observe all warnings and precautions listed for the product.

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8. Exposure Controls/Personal Protection

Airborne Exposure Limits:
None established.
Ventilation System:
A system of local and/or general exhaust is recommended to keep employee exposures as low as possible. Local exhaust ventilation is generally preferred because it can control the emissions of the contaminant at its source, preventing dispersion of it into the general work area. Please refer to the ACGIH document, *Industrial Ventilation, A Manual of Recommended Practices*, most recent edition, for details.
Personal Respirators (NIOSH Approved):
For conditions of use where exposure to dust or mist is apparent and engineering controls are not feasible, a particulate respirator (NIOSH type N95 or better filters) may be worn. If oil particles (e.g. lubricants, cutting fluids, glycerine, etc.) are present, use a NIOSH type R or P filter. For emergencies or instances where the exposure levels are not known, use a full-face positive-pressure, air-supplied respirator. WARNING: Air-purifying respirators do not protect workers in oxygen-deficient atmospheres.
Skin Protection:
Wear protective gloves and clean body-covering clothing.
Eye Protection:
Use chemical safety goggles. Maintain eye wash fountain and quick-drench facilities in work area.
Other Control Measures:
There is insufficient data in the published literature to assign complete numerical SAF-T-DATA* ratings and laboratory protective equipment for this product. Special

precautions must be used in storage, use and handling. Protective equipment for laboratory bench use should be chosen using professional judgment based on the size and type of reaction or test to be conducted and the available ventilation, with overriding consideration to minimize contact with the chemical.

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9. Physical and Chemical Properties

Appearance:
White powder.
Odor:
Odorless.
Solubility:
Soluble in water.
Specific Gravity:
No information found.
pH:
6.0-7.5 (1% aqueous solution)
% Volatiles by volume @ 21C (70F):
0
Boiling Point:
No information found.
Melting Point:
No information found.
Vapor Density (Air=1):
No information found.
Vapor Pressure (mm Hg):
0 @ 20C (68F)
Evaporation Rate (BuAc=1):
0

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10. Stability and Reactivity

Stability:
Stable under ordinary conditions of use and storage. Hygroscopic.
Hazardous Decomposition Products:
Burning may produce carbon monoxide, carbon dioxide, sulfur oxides, and nitrogen oxides.
Hazardous Polymerization:
Will not occur.
Incompatibilities:
Strong oxidizers.
Conditions to Avoid:
Heat, flames, ignition sources and incompatibles.

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11. Toxicological Information

Oral rat LD50: > 6 gm/kg. Investigated as a reproductive effector.

--------\Cancer Lists\----------

Ingredient	---NTP Carcinogen--- Known	Anticipated	IARC Category
Sodium Heparin (9041-08-1)	No	No	None

12. Ecological Information

Environmental Fate:
No information found.
Environmental Toxicity:
No information found.

13. Disposal Considerations

Whatever cannot be saved for recovery or recycling should be managed in an appropriate and approved waste disposal facility. Processing, use or contamination of this product may change the waste management options. State and local disposal regulations may differ from federal disposal regulations. Dispose of container and unused contents in accordance with federal, state and local requirements.

14. Transport Information

Not regulated.

15. Regulatory Information

--------\Chemical Inventory Status - Part 1\----------

Ingredient	TSCA	EC	Japan	Australia
Sodium Heparin (9041-08-1)	Yes	No	No	Yes

--------\Chemical Inventory Status - Part 2\----------

Ingredient	Korea	--Canada-- DSL	NDSL	Phil.
Sodium Heparin (9041-08-1)	No	Yes	No	No

--------\Federal, State & International Regulations - Part 1\----------

Ingredient	-SARA 302- RQ	TPQ	------SARA 313------ List	Chemical Catg.
Sodium Heparin (9041-08-1)	No	No	No	No

--------\Federal, State & International Regulations - Part 2\----------

	-RCRA-	-TSCA-

Ingredient	CERCLA	261.33	8(d)
Sodium Heparin (9041-08-1)	No	No	No

Chemical Weapons Convention: No TSCA 12(b): No CDTA: No
SARA 311/312: Acute: Yes Chronic: No Fire: No Pressure: No
Reactivity: No (Pure / Solid)

Australian Hazchem Code: None allocated.
Poison Schedule: None allocated.
WHMIS:
This MSDS has been prepared according to the hazard criteria of the Controlled Products Regulations (CPR) and the MSDS contains all of the information required by the CPR.

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16. Other Information

NFPA Ratings: Health: **1** Flammability: **1** Reactivity: **0**
Label Hazard Warning:
WARNING! MAY BE HARMFUL IF SWALLOWED, INHALED OR ABSORBED THROUGH SKIN. MAY CAUSE IRRITATION TO SKIN, EYES, AND RESPIRATORY TRACT.
Label Precautions:
No SAF-T-DATA Ratings have been developed for this product. Read and follow all warnings, precautions, instructions and other safety and handling information on the label and MSDS.
Avoid breathing dust.
Avoid contact with eyes, skin and clothing.
Keep container closed.
Use with adequate ventilation.
Wash thoroughly after handling.
Label First Aid:
In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Wash clothing before reuse. If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. If swallowed, give large amounts of water to drink. Never give anything by mouth to an unconscious person. In all cases, get medical attention.
Product Use:
Laboratory Reagent.
Revision Information:
MSDS Section(s) changed since last revision of document include: 8.
Disclaimer:
****

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